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Trauma Disclosure Moderates the Effects of Oxytocin on Intrusions and Neural Responses to Fear

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Posttraumatic stress disorder (PTSD) is a highly pernicious, disabling and frequently chronic condition. Current perspectives on the underlying neurocircuitry emphasize hyperreactivity of the amygdala and concomitant hyporeactivity of the prefrontal cortex (PFC) in response to trauma- and fear-associated stimuli [1]. Unlike most other psychiatric disorders, a PTSD diagnosis requires a clearly identifiable inciting event. As such, a number of psychosocial and somatic preventive interventions have been tested in recently traumatized individuals [2]. Neuroendocrinological targets include the hypothalamic peptide oxytocin (OXT). Currently, there is conflicting evidence whether or not early posttrauma administration of OXT could be effective in reducing PTSD-like symptoms in victims of recent traumatic experiences [3]. Furthermore, it is increasingly recognized that the prosocial and anxiolytic effects of intranasal OXT are moderated by context factors [4]. As a consequence, a better translation into clinical efficacy is currently hampered by limited mechanistic insights into how OXT influences traumatic experience.

The rationale of the present randomized, double-blind, placebo (PLC)-controlled, between-subject study was to combine a prospective experimental tool, the analogue trauma model, with a multimodal analysis strategy, to identify the underlying neurocircuitry effects of prolonged OXT administration early after trauma in a standardized setting where context factors can be rigorously controlled. An important context factor is trauma disclosure, which reduces distress by facilitating social support and by promoting integration and extinction of the traumatic memories [5]. Sixty-two healthy women (mean age \pm SD, 23.31 \pm 4.20 years) received intranasal OXT or PLC for 6 consecutive days and were confronted with a trauma movie on day 0 (before the treatment) and day 3 (after 3 days of treatment). Online diaries were used to

record intrusive memories and trauma disclosure patterns during these 6 days ($n = 31$ participants with strong trauma disclosure). After experimental trauma exposure on day 0 and again on day 3, participants completed an emotional face-matching functional magnetic resonance imaging task that we proved was sensitive to detect potentiated amygdala responses in the aftermath of the experimental trauma (see suppl. information; for all online suppl. material, see www.karger.com/doi/10.1159/000496056). We hypothesized that OXT would decrease intrusive symptoms accompanied by enhanced PFC activation and concomitantly reduced amygdala responses to fearful faces [6]. Given evidence for an interaction between OXT and social support [7], we further expected that the anxiolytic effects of OXT would be more pronounced in combination with strong trauma disclosure.

Under PLC, the total number of intrusions in the 3 days after the first trauma exposure was positively associated with the need to discuss the movie ($r_{30} = 0.74, p < 0.01$) and with the actual time spent discussing it ($r_{30} = 0.63, p < 0.01$). It thus appears that higher posttrauma symptom loads served as efficient triggers for trauma self-disclosure. OXT did not significantly alter the need to discuss the movie or the time spent discussing it (all p values > 0.10). The number of intrusions declined over time ($F_{1,50, 82.54} = 30.21, p < 0.01, \eta_p^2 = 0.36$), but there was no main or interaction effect of treatment in the whole sample (all p values > 0.55). However, an analysis of variance with the additional factor trauma disclosure (strong, weak) revealed a significant interaction between treatment and trauma disclosure ($F_{1,53} = 4.82, p = 0.03, \eta_p^2 = 0.08$). Post hoc t tests showed that OXT significantly reduced the total number of intrusions in participants exhibiting strong trauma disclosure ($t_{21.72} = -2.17, p = 0.04, d = -0.82$) (cf. Fig. 1a) but had the opposite, although nonsignificant, effect in participants with weak trauma disclosure ($t_{29} = 1.07, p = 0.30, d = 0.40$). Interestingly, participants displaying weak trauma disclosure had lower salivary OXT concentrations after the trauma movie than participants with strong trauma disclosure (day 0: $t_{36.13} = -2.24, p = 0.03, d = -0.63$; day 3 PLC: $t_{25} = -2.18, p = 0.04, d = -0.87$; see suppl. information).

In participants with strong trauma disclosure, OXT enhanced responses to fearful faces in the left middle frontal cortex (peak MNI coordinates $x, y, z: -36, 46, 0, t_{56} = 4.44, p$ value of family-wise error, $p_{FWE} = 0.04$; cf. Fig. 1b). By contrast, OXT significantly decreased activations in the right medial frontal cortex ($10, 54, -6, t_{52} = 4.17, p_{FWE} = 0.03$) in response to fearful faces in participants with weak trauma disclosure. In a next step, we examined possible treatment effects on functional connectivity and found that OXT increased functional coupling between the middle frontal cortex as seed region and the left amygdala ($-26, 0, -16, t_{56} = 3.58, p_{FWE} = 0.03$; cf. Fig. 1c) for fearful faces in participants with strong trauma disclosure. OXT had no effect on the functional connectivity between these regions in participants with weak trauma disclosure.

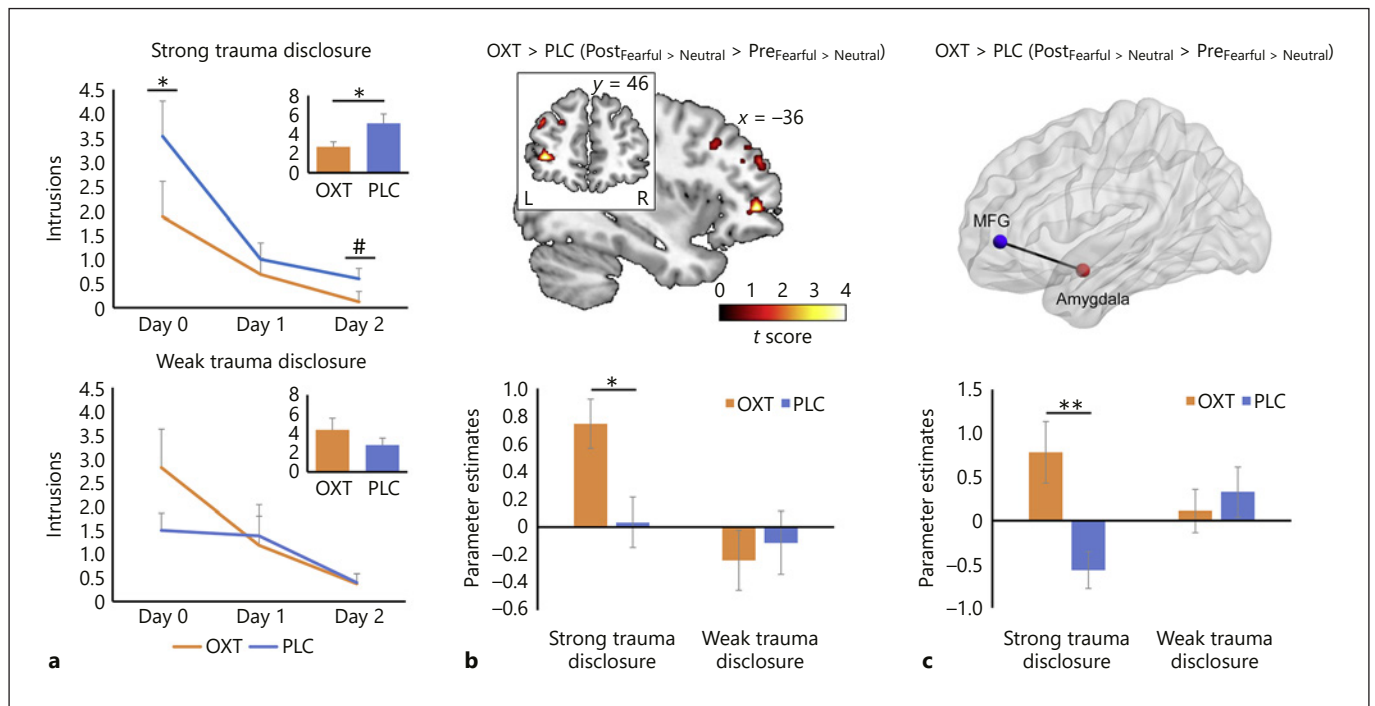


Fig. 1. Intranasal oxytocin (OXT) compared to placebo (PLC) significantly reduced the number of trauma-induced intrusions in participants with strong trauma disclosure (i.e., at least 2 discussions about the first trauma movie) after the first trauma exposure, but nonsignificantly increased the number of intrusions after the first trauma exposure in participants with weak trauma disclosure (a). Insets display the average sum of intrusions in the 3 days after trauma exposure. At the neural level, intranasal OXT over 3 days significantly increased responses to fearful faces in the middle frontal cortex in participants with strong trauma disclosure (b). OXT also increased the functional connectivity between the left middle frontal cortex as seed region and the left amygdala in response to fearful faces compared to neutral faces (c). Error bars indicate the standard error of the mean. MFG, middle frontal gyrus; OXT, oxytocin; PLC, placebo; Post, fMRI assessment after treatment; Pre, fMRI assessment before treatment; # $p < 0.10$, * $p < 0.05$, ** $p < 0.01$.

tral faces in the middle frontal cortex in participants with strong trauma disclosure (b). OXT also increased the functional connectivity between the left middle frontal cortex as seed region and the left amygdala in response to fearful faces compared to neutral faces (c). Error bars indicate the standard error of the mean. MFG, middle frontal gyrus; OXT, oxytocin; PLC, placebo; Post, fMRI assessment after treatment; Pre, fMRI assessment before treatment; # $p < 0.10$, * $p < 0.05$, ** $p < 0.01$.

Our finding of differential OXT effects depending on trauma disclosure patterns supports current views that OXT enhances the salience of social signals [8] and that context factors determine the outcome of OXT treatment protocols [4]. Specifically, OXT mediates the stress-buffering effects of social support [7], but it also exacerbates subjective feelings of psychosocial stress if social support is not available [9]. Thus, our finding of OXT-induced increases in PFC responses to fearful stimuli suggests that OXT treatment after trauma exposure may enhance the salience of positive social interactions and strengthen the extinction of intrusive memories via top-down control descending from the PFC to the amygdala.

Participants with strong trauma disclosure in the PLC group experienced more intrusive memories, despite higher endogenous OXT levels after the trauma movie. Thus, the higher symptom load in combination with elevated OXT levels may have caused the participants to discuss the traumatic event and seek social support [10]. However, elevated OXT levels alone are not sufficient to induce trauma disclosure because intranasal OXT did not increase a propensity for trauma disclosure. This notion has important translational implications in suggesting that more robust clinical effects of OXT treatments after trauma exposure may require strict con-

trol of the therapeutic context including trauma disclosure. Future studies are warranted to examine the combination of OXT with supportive interventions that enable trauma disclosure in a safe context.

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Disclosure Statement

The authors report no competing biomedical financial interests or personal affiliations in connection with the content of this manuscript.

Author Contributions

D.S. and R.H. designed the experiments; D.S., J.L., A.P., C.E. and L.S. conducted the experiments; D.S., J.L., A.P., C.E., L.S. and R.H. analyzed the data; all authors contributed to writing the paper.

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